04/2004

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STRUCTURE FILE UPDATES:   20 JAN 2003  HIGHEST RN 479577-81-6
DICTIONARY FILE UPDATES:  20 JAN 2003  HIGHEST RN 479577-81-6

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PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d sqide can tot l41

L41  ANSWER 1 OF 4  REGISTRY  COPYRIGHT 2003 ACS
RN   473743-92-9  REGISTRY
CN   Phosphatase, protein phosphoserine/phosphothreonine, ILKAP (human clone
     C1) (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   2: PN: US20020156003 FIGURE: 1 claimed protein
FS   PROTEIN SEQUENCE
SQL  392

SEQ      1 MDLFGDLPEP ERSPRPAAGK EAQKGPLLFD DLPPASSTDS GSGGPLLFDD
        51 LPPASSGDSG SLATSISQMV KTEGKGAKRK TSEEEKNGSE ELVEKKVCKA
       101 SSVIFGLKGY VAERKGEREE MQDAHVILND ITEECRPPSS LITRVSYFAV
       151 FDGHGGIRAS KFAAQNLHQN LIRKFPKGDV ISVEKTVKRC LLDTFKHTDE
       201 EFLKQASSQK PAWKDGSTAT CVLAVDNILY IANLGDSRAI LCRYNEESQK
       251 HAALSLSKEH NPTQYEERMR IQKAGGNVRD GRVLGVLEVS RSIGDGQYKR
       301 CGVTSVPDIR RCQLTPNDRF ILLACDGLFK VFTPEEAVNF ILSCLEDEKI
       351 QTREGKSAAD ARYEAACNRL ANKAVQRGSA DNVTVMVVRI GH

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   CA, CAPLUS, USPATFULL
                  1 REFERENCES IN FILE CA (1962 TO DATE)
                  1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE   1:  137:321374

L41  ANSWER 2 OF 4  REGISTRY  COPYRIGHT 2003 ACS
RN   473743-91-8  REGISTRY
CN   DNA (human clone C1 protein phosphatase ILKAP (integrin-linked
     kinase-associated serine/threonine phosphatase 2C) cDNA plus flanks) (9CI)
     (CA INDEX NAME)
OTHER NAMES:
CN   1: PN: US20020156003 FIGURE: 1 claimed DNA
FS   NUCLEIC ACID SEQUENCE
SQL  1422
```

NA 344 a 355 c 403 g 320 t

SEQ
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      1 ggcaccaggc ccgctgctgc cgcccgcccg gggtgtggag cccggccgct
     51 gctcgcgggc tgagtgtctg tcgctgctgc cgcctccacc cagcctccgc
    101 catggacctc ttcggggacc tgccggagcc cgagcgctcg ccgcgcccgg
    151 ctgcccggaa agaagctcag aaaggacccc tgctctttga tgacctccct
    201 ccggccagca gtactgactc aggatcaggg ggacctttgc tttttgatga
    251 tctcccaccc gctagcagtg gcgattcagg ttctcttgcc acatcaatat
    301 cccagatggt aaagactgaa gggaaaggag caaagagaaa aacctccgag
    351 gaagagaaga atggcagtga agagcttgtg gaaaagaaag tttgtaaagc
    401 ctcttcggtg atctttggtc tgaagggcta tgtggctgag cggaagggtg
    451 agagggagga gatgcaggat gcccacgtca tcctgaacga catcaccgag
    501 gagtgtaggc ccccatcgtc cctcattact cgggtttcat attttgctgt
    551 ttttgatgga catggaggaa ttcgagcctc aaaatttgct gcacagaatt
    601 tgcatcaaaa cttaatcaga aaatttccta aaggagatgt aatcagtgta
    651 gagaaaaccg tgaagagatg ccttttggac actttcaagc atactgatga
    701 agagttcctt aaacaagctt ccagccagaa gcctgcctgg aaagatgggt
    751 ccactgccac gtctgttctg gctgtagaca acattcttta tattgccaac
    801 ctcggacata gtcgggcaat cttgtgtcgt tataatgagg agagtcaaaa
    851 acatgcagcc ttaagcctca gcaaagagca taatccaact cagtatcaag
    901 agccgatcag aatacagaag gctggaggaa acgtcaggga tgggcgtgtt
    951 ttgggcgtgc tagaggtgtc acgctccatt ggggacgggc agtacaagcg
   1001 ctgcggtgtc acctctgtgc cccacatcag acgctgccag ctgaccccca
   1051 atgacaggtt cattttgttg gcctgtgatg ggctcttcaa ggtctttacc
   1101 ccagaagaag ccgtgaactt catcttgtcc tgtctcgagg atgaaaagat
   1151 ccagacccgg gaagggaagt ccgcagccga cgcccgctac gaagcagcct
   1201 gcaacaggct ggccaacaag gcggtgcagc ggggctcggc cgacaacgtc
   1251 actgtgatgg tggtgcggat agggcactga ggggtggcgc gcggccagga
   1301 gcacgcatgg tattgactta aaaggttcat tttgtgtgtg tgcacattgt
   1351 gtgttttgtg tactcctgtg ggactcccat ggttgtaaat aaaggtttct
   1401 ctttttttc ctaaaaaaaa aa
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MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:321374

L41 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN **367924-80-9** REGISTRY
CN Phosphatase, protein phosphoserine/phosphothreonine, ILKAP (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Integrin-linked kinase-assocd. serine/threonine phosphatase 2C
CN Protein phosphatase ILKAP
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
2 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:321374

REFERENCE 2: 135:328611

L41 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN **173585-04-1** REGISTRY
CN Kinase (phosphorylating), protein p59ILK (9CI) (CA INDEX NAME)

OTHER NAMES:
CN .beta.1-Integrin-assocd. kinase
CN .beta.1-Integrin-linked protein kinase
CN Integrin-linked kinase
CN p59ILK Serine/threonine protein kinase
CN Protein kinase ILK
CN Protein p59ILK kinase
MF Unspecified
CI MAN
SR CA
LC STN Files: AGRICOLA, BIOSIS, CA, CAPLUS, CIN, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
98 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
99 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:20443

REFERENCE 2: 138:11409

REFERENCE 3: 138:319

REFERENCE 4: 137:365370

REFERENCE 5: 137:346244

REFERENCE 6: 137:323482

REFERENCE 7: 137:322993

REFERENCE 8: 137:304771

REFERENCE 9: 137:292146

REFERENCE 10: 137:241573

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(FILE 'HOME' ENTERED AT 07:33:53 ON 21 JAN 2003)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 07:34:21 ON 21 JAN 2003
E PHOSPHATASE/CN
L1 1 S E3
L2 11938 S PHOSPHATASE
L3 1 S L1 AND L2
L4 11937 S L2 NOT L3
E ILKAP
L5 5 S E3
L6 1 S 473743-92-9
L7 1 S L5 AND L6
L8 4 S L5 NOT L7

FILE 'HCAPLUS' ENTERED AT 07:35:59 ON 21 JAN 2003
L9 1 S L7

FILE 'REGISTRY' ENTERED AT 07:36:57 ON 21 JAN 2003
L10 1 S 473743-91-8
L11 1 S 367924-80-9

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     FILE 'HCAPLUS' ENTERED AT 07:37:17 ON 21 JAN 2003
L12           1 S L10
L13           2 S L11
L14           2 S L9,L12,L13
                E ILKAP
L15           2 S E3
L16          15 S INTEGRIN(L)LINK?(L)?KINASE?(L)ASSOC?(L)?PHOSPHATASE?
L17           8 S L16 (L) SERIN?(L)THREON?
L18           7 S L16 NOT L17
L19           2 S L14,L15
L20           2 S L19 AND L17
L21           6 S L17 NOT L20
L22           4 S L16 AND ILK
L23           5 S L16 AND INTEGRIN LINK? ?KINASE?
L24           5 S L22,L23
L25           2 S L20 AND L24
L26           5 S ILK? AND L12-L25

     FILE 'REGISTRY' ENTERED AT 07:46:43 ON 21 JAN 2003
L27           1 S 173585-04-1

     FILE 'HCAPLUS' ENTERED AT 07:46:55 ON 21 JAN 2003
L28          99 S L27
L29           3 S L28 AND L12-L26
L30           5 S L24-L26,L29
                SEL DN AN L30 1 3 5
L31           2 S L30 NOT E1-E5
                E LORENS J/AU
L32          29 S E4-E6
                E XU W/AU
L33         423 S E3-E22
                E XU WEI/AU
L34         465 S E3
                E XU WEIDUAN/AU
L35           6 S E3
                E ATCHISON R/AU
L36          16 S E3,E4,E9-E10
                E BOGENBERGER J/AU
L37          27 S E3-E8
                E RIGEL/PA,CS
L38          91 S E3-E19
L39           1 S L32-L38 AND L9,L12-L26,L28-L31
L40           2 S L31,L39
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 07:50:51 ON 21 JAN 2003
L41           4 S E1-E4

     FILE 'BIOSIS' ENTERED AT 07:51:00 ON 21 JAN 2003
L42           0 S L7 OR L10
L43         125 S L27
                E ILKAP
L44           2 S E3
                E ILK
L45           8 S L17
                SEL DN AN 4
L46           1 S L45 AND E1-E2
L47           2 S L44,L46
L48           6 S ILK?(L)ASSOC?(L)?PHOSPHATASE?
L49           2 S L47 AND L48
L50           4 S L43 AND L48
L51           2 S L49,L47
L52           4 S L50 NOT L51
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L53           2 S L51 AND L42-L52
                E LORENS J/AU
L54          34 S E3-E6
                E XU W/AU
L55         406 S E3-E22
                E XU WEI/AU
L56         107 S E3
L57           7 S E34
                E ATCHISON R/AU
L58          28 S E3,E5,E9-E11
                E BOGENBERGER J/AU
L59          35 S E3-E7
L60           0 S L43-L53 AND L54-L59

     FILE 'MEDLINE' ENTERED AT 07:57:37 ON 21 JAN 2003
L61           0 S L7 OR L10
                E ILKAP
L62           1 S E3
L63          98 S INTEGRIN? LINK? ?KINASE?
L64          28 S L63 (L) SERIN?(L)THREON?
L65           6 S L64 (L) ?PHOSPHATASE?
                SEL DN AN 4 5 6
L66           3 S E1-E9 AND L65
L67           3 S L62,L66

     FILE 'WPIX' ENTERED AT 08:00:13 ON 21 JAN 2003
                E ILKAP
L68           0 S L65

     FILE 'BIOTECHDS' ENTERED AT 08:00:39 ON 21 JAN 2003
                E ILKAP
L69           0 S INTEGRIN?(L)LINK?(L)KINASE?(L)PHOSPHATASE(L)SERIN?(L)THREON?

     FILE 'REGISTRY' ENTERED AT 08:01:47 ON 21 JAN 2003

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FILE LAST UPDATED: 20 Jan 2003  (20030120/ED)

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 substance identification.


=> d l40 all tot

L40  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2003 ACS
AN   2002:814830  HCAPLUS
```

DN 137:321374
TI Use of **integrin-linked kinase** associated protein in regulation of angiogenesis
IN **Lorens, James B.; Xu, Weiduan; Atchison, Robert E.; Bogenberger, Jakob**
PA **Rigel Pharmaceuticals, Inc., USA**
SO U.S. Pat. Appl. Publ., 20 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM C12Q001-68
ICS G01N033-53; A61K039-395; G01N033-567; A61K038-17
NCL 514012000
CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 1, 7, 13, 14
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002156003	A1	20021024	US 2001-935124	20010821
	WO 2002085289	A2	20021031	WO 2002-US12341	20020418

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-284760P P 20010418
US 2001-935124 A 20010821

AB The present invention relates to regulation of angiogenesis. More particularly, the present invention is directed to nucleic acids encoding C1-angiogenesis protein, also called **integrin-linked kinase-assocd. serine/threonine phosphatase** 2C ("**ILKAP**") and **ILKAP** protein, which is involved in modulation of angiogenesis. The invention further relates to methods for identifying and using agents, including small org. mols., antibodies, peptides, cyclic peptides, nucleic acids, antisense nucleic acids, and ribozymes, that modulate angiogenesis via modulation of **ILKAP** and **ILKAP**-related cascades; as well as to the use of expression profiles and compns. in diagnosis and therapy of angiogenesis.

ST **integrin linked kinase assocd serine threonine phosphatase** 2C therapy; human cDNA sequence **ILKAP; ILKAP** protein angiogenesis therapy

IT Angiogenic factors
Growth inhibitors, animal
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(angiogenic growth-inhibiting factors, **ILKAP** as; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(avb3, **ILKAP** in regulation of; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)

IT Ligands
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(binding to **ILKAP**; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)

IT Blood vessel
(endothelium, **ILKAP** synthesis in; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT cDNA sequences
(for **ILKAP** of human; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT Drug screening
(for **ILKAP** protein effectors; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT Peptides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for **ILKAP** protein; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT Gene therapy
(for angiogenesis-related disorders; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT cDNA
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for **integrin-linked kinase** assocd. protein; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT Chemotaxis
(haptotaxis, **ILKAP** in regulation of endothelial cell; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal, to **ILKAP** protein; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT Molecular cloning
(of **ILKAP** cDNA; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT Protein sequences
(of **ILKAP** of human; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT Human
(regulation of angiogenesis in; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT Organic compounds, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small, binding to **ILKAP** protein; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT Probes (nucleic acid)
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(to **ILKAP** cDNA; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT Antisense DNA
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to **ILKAP** cDNA; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to **ILKAP** protein; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)
IT Angiogenesis

Nucleic acid hybridization
(use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)

IT **473743-92-9**
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino acid sequence; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)

IT **473743-91-8**
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nucleotide sequence; use of **integrin-linked kinase** assocd. protein in regulation of angiogenesis)

IT **367924-80-9, Integrin-linked kinase-assocd. serine/threonine phosphatase 2C**
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of **integrin-linked kinase assocd.** protein in regulation of angiogenesis)

L40 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:379396 HCAPLUS
DN 135:328611
TI Modulation of **integrin** signal transduction by **ILKAP**, a protein **phosphatase** 2C **associating** with the **integrin-linked kinase, ILK1**
AU Leung-Hagesteijn, Chungyee; Mahendra, Ahalya; Naruszewicz, Izabela; Hannigan, Gregory E.
CS Programme in Cell Biology, Research Institute, Hospital for Sick Children, Toronto, ON, M5G 1X8, Can.
SO EMBO Journal (2001), 20(9), 2160-2170
CODEN: EMJODG; ISSN: 0261-4189
PB Oxford University Press
DT Journal
LA English
CC 7-2 (Enzymes)
Section cross-reference(s): 3, 13
AB **ILKAP**, a protein **serine/threonine** (S/T) **phosphatase** of the PP2C family, was isolated in a yeast two-hybrid screen baited with **integrin-linked kinase, ILK1**. **Assocn.** of **ILK1** and **ILKAP** was independent of the catalytic activity of either partner, as assayed in co-pptn. and two-hybrid expts. Conditional expression of **ILKAP** in HEK 293 cells resulted in selective inhibition of ECM- and growth factor-stimulated **ILK1** activity, but did not inhibit Raf-1 **kinase** activity. A catalytic mutant of **ILKAP**, H154D, did not inhibit **ILK1 kinase** activity. Two cellular targets of **ILK1**, glycogen synthase **kinase** 3 .beta. (GSK3.beta.) and protein **kinase** B (PKB)/AKT, were differentially affected by **ILKAP**-mediated inhibition of **ILK1**. Catalytically active, but not mutant **ILKAP**, strongly inhibited insulin-like growth factor-1-stimulated GSK3.beta. phosphorylation on Ser9, but did not affect phosphorylation of PKB on Ser473, suggesting that **ILKAP** selectively affects **ILK**-mediated GSK3.beta. signaling. Consistent with this, active, but not H154D mutant or the related PP2C.alpha., selectively inhibited transactivation of a Tcf/Lef reporter gene, TOPFlash, in 293 cells. We propose that **ILKAP** regulates **ILK1** activity, targeting **ILK1** signaling of Wnt pathway components via modulation of GSK3.beta. phosphorylation.
ST **integrin linked kinase assocd** protein **phosphatase** 2C **ILKAP**; **ILKAP** human cDNA sequence

IT Molecular **association**
Protein sequences
Signal transduction, biological
cDNA sequences
(cloning, sequence and signal transduction properties of **ILKAP**, a protein **phosphatase** 2C **assocg.** with **integrin-linked kinase, ILK1**)

IT 301802-70-0
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(amino acid sequence; cloning, sequence and signal transduction properties of **ILKAP**, a protein **phosphatase** 2C **assocg.** with **integrin-linked kinase**, **ILK1**)

IT **367924-80-9, Integrin-linked kinase-assocd. serine/threonine phosphatase** 2C
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(cloning, sequence and signal transduction properties of **ILKAP**, a protein **phosphatase** 2C **assocg.** with **integrin-linked kinase, ILK1**)

IT **173585-04-1, Integrin-linked kinase**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cloning, sequence and signal transduction properties of **ILKAP**, a protein **phosphatase** 2C **assocg.** with **integrin-linked kinase, ILK1**)

IT 328895-62-1, GenBank AY024365
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; cloning, sequence and signal transduction properties of **ILKAP**, a protein **phosphatase** 2C **assocg.** with **integrin-linked kinase**, **ILK1**)

RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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=> fil biosis
FILE 'BIOSIS' ENTERED AT 08:02:36 ON 21 JAN 2003

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 15 January 2003 (20030115/ED)

=> d l53 all tot

L53 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:165411 BIOSIS
DN PREV200200165411
TI Modulation of integrin signal transduction by **ILKAP**, an **ILK-associated** protein **phosphatase** 2C.
AU Hannigan, Greg E. (1); Mahendra, Ahalya (1); Leung-Hagesteijn, Chungyee (1); Naruszewicz, Izabela (1); Wang, Ping (1)
CS (1) Cell Biology Program, Hospital for Sick Children, 555 University Ave, Toronto, ON, M5G 1X8 Canada
SO Molecular Biology of the Cell, (Nov, 2001) Vol. 12, No. Supplement, pp. 323a. http://www.molbiolcell.org/. print.
Meeting Info.: 41st Annual Meeting of the American Society for Cell Biology Washington DC, USA December 08-12, 2001
ISSN: 1059-1524.
DT Conference
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
Cytology and Cytochemistry - General *02502
Cytology and Cytochemistry - Animal *02506
Cytology and Cytochemistry - Human *02508
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Enzymes - General and Comparative Studies; Coenzymes *10802
Endocrine System - General *17002
BC Hominidae 86215
Muridae 86375
IT Major Concepts
Cell Biology; Enzymology (Biochemistry and Molecular Biophysics)
IT Parts, Structures, & Systems of Organisms
extracellular matrix [ECM]
IT Chemicals & Biochemicals
GSK3-beta [glycogen synthase kinase 3-beta]: phosphorylation; IGF-1 [insulin-like growth factor-1]: phosphorylation; **ILKAP** [integrin-linked kinase **associated** protein]; PKB [protein kinase B]; PP2C-alpha [protein **phosphatase** 2C-alpha]; Tcf/Lef-1 factors: activation; integrin; interferon; intergrin-linked kinase 1 [**ILK1**]; **phosphatase** 2C; red fluorescent fusion protein; serine-473; serine-9
IT Methods & Equipment

co-precipitation experiment: experimental method, separation method; yeast two-hybrid screen: screening method

IT Miscellaneous Descriptors
ISRE-dependent transcription; Wnt pathway; signal transduction: modulation; Meeting Abstract

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
HEK 293 cell line (Hominidae): human embyronic kidney cells; L6 cell line (Muridae): rat myoblast cells; rat (Muridae)

ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Primates; Rodents; Vertebrates

RN 67763-96-6 (INSULIN-LIKE GROWTH FACTOR-1)
148640-14-6 (PROTEIN KINASE B)
153-87-7Q (INTEGRIN)
60791-49-3Q (INTEGRIN)

L53 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN **2001:313654** BIOSIS
DN **PREV200100313654**
TI Modulation of integrin signal transduction by **ILKAP**, a protein **phosphatase** 2C **associating** with the integrin-linked kinase, **ILK1**.
AU Leung-Hagesteijn, Chungyee; Mahendra, Ahalya; Naruszewicz, Izabela; Hannigan, Gregory E. (1)
CS (1) Programme in Cell Biology, Research Institute, Hospital for Sick Children, 555 University Avenue, Toronto, ON, M5G 1X8: hannigan@sickkids.on.ca Canada
SO EMBO (European Molecular Biology Organization) Journal, (May 1, 2001) Vol. 20, No. 9, pp. 2160-2170. print.
ISSN: 0261-4189.
DT Article
LA English
SL English
AB **ILKAP**, a protein **serine/threonine** (S/T) **phosphatase** of the PP2C family, was isolated in a yeast two-hybrid screen baited with **integrin-linked kinase**, **ILK1**. **Association** of **ILK1** and **ILKAP** was independent of the catalytic activity of either partner, as assayed in co-precipitation and two-hybrid experiments. Conditional expression of **ILKAP** in HEK 293 cells resulted in selective inhibition of ECM- and growth factor-stimulated **ILK1** activity, but did not inhibit Raf-1 **kinase** activity. A catalytic mutant of **ILKAP**, H154D, did not inhibit **ILK1 kinase** activity. Two cellular targets of **ILK1**, glycogen synthase **kinase** 3 beta (GSK3beta) and protein **kinase** B (PKB)/AKT, were differentially affected by **ILKAP**-mediated inhibition of **ILK1**. Catalytically active, but not mutant **ILKAP**, strongly inhibited insulin-like growth factor-1-stimulated GSK3beta phosphorylation on Ser9, but did not affect phosphorylation of PKB on Ser473, suggesting that **ILKAP** selectively affects **ILK** -mediated GSK3beta signalling. Consistent with this, active, but not H154D mutant or the related PP2Calpha, selectively inhibited transactivation of a Tcf/Lef reporter gene, TOPFlash, in 293 cells. We propose that **ILKAP** regulates **ILK1** activity, targeting **ILK1** signalling of Wnt pathway components via modulation of GSK3beta phosphorylation.
CC Cytology and Cytochemistry - General *02502
Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Human *03508
Biochemical Studies - Proteins, Peptides and Amino Acids *10064

Enzymes - General and Comparative Studies; Coenzymes *10802
Endocrine System - General *17002
BC Hominidae 86215
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Cell Biology
IT Parts, Structures, & Systems of Organisms
cell
IT Chemicals & Biochemicals
Wnt; glycogen synthase kinase-3-beta; insulin-like growth factor-1; integrin-linked kinase-1; integrin-linked kinase-1-associated phosphatase: protein phosphatase 2C; protein kinase B
IT Methods & Equipment
yeast two-hybrid screening: purification method
IT Miscellaneous Descriptors
signal transduction
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
293 cell line (Hominidae)
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN 67763-96-6 (INSULIN-LIKE GROWTH FACTOR-1)
148640-14-6 (PROTEIN KINASE B)
GEN TOPFlash gene: reporter gene

=> fil medline
FILE 'MEDLINE' ENTERED AT 08:02:43 ON 21 JAN 2003

FILE LAST UPDATED: 18 JAN 2003 (20030118/UP). FILE COVERS 1958 TO DATE.

On June 9, 2002, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2003 vocabulary. See http://www.nlm.nih.gov/mesh/summ2003.html for a description on changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all tot l67

L67 ANSWER 1 OF 3 MEDLINE
AN **2001272332** MEDLINE
DN **21231163** PubMed ID: **11331582**
TI Modulation of integrin signal transduction by **ILKAP**, a protein phosphatase 2C associating with the integrin-linked kinase, ILK1.
AU Leung-Hagesteijn C; Mahendra A; Naruszewicz I; Hannigan G E
CS Programme in Cell Biology, Research Institute, Hospital for Sick Children, 555 University Avenue, Toronto, ON, M5G 1X8, Canada.
SO EMBO JOURNAL, (2001 May 1) 20 (9) 2160-70.
Journal code: 8208664. ISSN: 0261-4189.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AY024365
EM 200105
ED Entered STN: 20010604
Last Updated on STN: 20021218
Entered Medline: 20010531
AB **ILKAP**, a protein **serine/threonine** (S/T) **phosphatase** of the PP2C family, was isolated in a yeast two-hybrid

screen baited with **integrin-linked kinase**, ILK1. Association of ILK1 and **ILKAP** was independent of the catalytic activity of either partner, as assayed in co-precipitation and two-hybrid experiments. Condi tional expression of **ILKAP** in HEK 293 cells resulted in selective inhibition of ECM- and growth factor-stimulated ILK1 activity, but did not inhibit Raf-1 kinase activity. A catalytic mutant of **ILKAP**, H154D, did not inhibit ILK1 kinase activity. Two cellular targets of ILK1, glycogen synthase kinase 3 beta (GSK3beta) and protein kinase B (PKB)/AKT, were differentially affected by **ILKAP**-mediated inhibition of ILK1. Catalytically active, but not mutant **ILKAP**, strongly inhibited insulin-like growth factor-1-stimulated GSK3beta phosphorylation on Ser9, but did not affect phosphorylation of PKB on Ser473, suggesting that **ILKAP** selectively affects ILK-mediated GSK3beta signalling. Consistent with this, active, but not H154D mutant or the related PP2Calpha, selectively inhibited transactivation of a Tcf/Lef reporter gene, TOPFlash, in 293 cells. We propose that **ILKAP** regulates ILK1 activity, targeting ILK1 signalling of Wnt pathway components via modulation of GSK3beta phosphorylation.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.
Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism
Carrier Proteins: GE, genetics
*Carrier Proteins: ME, metabolism
Catalysis
Cell Line
Gene Expression
Genes, Reporter
Glycogen Synthase Kinase 3
Glycogen Synthase Kinases
Insulin-Like Growth Factor I: ME, metabolism
Insulin-Like Growth Factor I: PD, pharmacology
*Integrins: ME, metabolism
Isoenzymes: GE, genetics
Isoenzymes: ME, metabolism
Kidney: CY, cytology
Kidney: ME, metabolism
Molecular Sequence Data
Mutagenesis, Site-Directed
Phosphoprotein Phosphatase: GE, genetics
*Phosphoprotein Phosphatase: ME, metabolism
Phosphorylation: DE, drug effects
Protein-Serine-Threonine Kinases: AI, antagonists & inhibitors
*Protein-Serine-Threonine Kinases: ME, metabolism
Proto-Oncogene Proteins: ME, metabolism
Proto-Oncogene Proteins c-raf: ME, metabolism
Sequence Homology, Amino Acid
*Signal Transduction: PH, physiology
Trans-Activation (Genetics): DE, drug effects
Transfection
Two-Hybrid System Techniques

RN 67763-96-6 (Insulin-Like Growth Factor I)

CN 0 (Carrier Proteins); 0 (IKAP protein); 0 (Integrins); 0 (Isoenzymes); 0 (Proto-Oncogene Proteins); 0 (proto-oncogene protein akt); EC 2.7.1.- (integrin-linked kinase); EC 2.7.1.123 (Ca(2+)-Calmodulin Dependent Protein Kinase); EC 2.7.1.37 (Glycogen Synthase Kinase 3); EC 2.7.1.37 (Glycogen Synthase Kinases); EC 2.7.1.37 (Protein-Serine-Threonine Kinases); EC 2.7.1.37 (Proto-Oncogene Proteins c-raf); EC 3.1.3.- (protein phosphatase 2C); EC 3.1.3.16 (Phosphoprotein Phosphatase)

L67 ANSWER 2 OF 3 MEDLINE
AN **2001013612** MEDLINE
DN **20464902** PubMed ID: **11007949**

TI Integrin-linked kinase (ILK): a "hot" therapeutic target.
AU Yoganathan T N; Costello P; Chen X; Jabali M; Yan J; Leung D; Zhang Z; Yee A; Dedhar S; Sanghera J
CS Kinetek Pharmaceuticals Inc., Vancouver, BC V6P6P2, Canada.. nathan@kinetekpharm.com
SO BIOCHEMICAL PHARMACOLOGY, (2000 Oct 15) 60 (8) 1115-9. Ref: 26
Journal code: 0101032. ISSN: 0006-2952.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200010
ED Entered STN: 20010322
Last Updated on STN: 20020420
Entered Medline: 20001031
AB Integrin-mediated cell adhesion is known to regulate gene expression through the activation of transcription factors. We have recently revealed that these activations are mediated through **integrin-linked kinase** (ILK). ILK is an ankyrin repeat-containing **serine-threonine** protein kinase that can interact directly with the cytoplasmic domain of the beta1 and beta3 integrin subunits and whose kinase activity is modulated by cell-extracellular matrix interactions. We have shown that ILK overexpression results in the translocation of beta-catenin to the nucleus, which then forms a complex formation with the lymphoid enhancer binding factor 1 (LEF-1) transcription factor, subsequently activating the transcriptional activity of promoters containing LEF-1 response elements. ILK phosphorylates the glycogen synthase kinase-3 (GSK-3), which inhibits GSK-3 activity. We have demonstrated that ILK stimulates activator protein-1 transcriptional activity through GSK-3 and the subsequent regulation of the c-Jun-DNA interaction. ILK also phosphorylates protein kinase B (PKB/Akt) and stimulates its activity. We have shown that ILK is an upstream effector of the phosphatidylinositol 3-kinase-dependent regulation of PKB/Akt. ILK has been shown to phosphorylate PKB/Akt on Ser-473 in vitro and in vivo. Our results clearly indicate that ILK is a key element in the regulation of integrin signaling as well as growth factor and Wnt signaling pathways. PTEN (**phosphatase** and tensin homolog detected on chromosome 10) is a tumor suppressor gene located on chromosome 10q23 that encodes a protein and phospholipid **phosphatase**. It is now estimated that inactivation mutants of PTEN exist in 60% of all forms of solid tumors. Loss of expression or mutational inactivation of PTEN leads to the constitutive activation of PKB/Akt via enhanced phosphorylation of Thr-308 and Ser-473. We have demonstrated that the activity of ILK is constitutively elevated in PTEN mutant cells. A small molecule ILK inhibitor suppresses the phosphorylation of PKB at the Ser-473 but not the Thr-308 site in the PTEN mutant cells. These results indicate that inhibition of ILK may be of significant value in solid tumor therapy.
CT Check Tags: Animal; Human
Cell Movement: PH, physiology
Cell Survival: DE, drug effects
Cell Survival: PH, physiology
Enzyme Activation
Enzyme Inhibitors: PD, pharmacology
*Integrins: PH, physiology
Phosphoprotein Phosphatase: ME, metabolism
Protein-Serine-Threonine Kinases: AI, antagonists & inhibitors
*Protein-Serine-Threonine Kinases: ME, metabolism
Protein-Serine-Threonine Kinases: PH, physiology
*Signal Transduction: PH, physiology
CN 0 (Enzyme Inhibitors); 0 (Integrins); EC 2.7.1.- (Protein-Serine-Threonine Kinases); EC 2.7.1.- (integrin-linked kinase); EC 3.1.3.16 (Phosphoprotein

Phosphatase)

L67 ANSWER 3 OF 3 MEDLINE
AN **2000105777** MEDLINE
DN **20105777** PubMed ID: **10637513**
TI Integrin-linked kinase regulates phosphorylation of serine 473 of protein kinase B by an indirect mechanism.
AU Lynch D K; Ellis C A; Edwards P A; Hiles I D
CS Department of Pathology, Cambridge Unversity, Tennis Court Road, Cambridge CB2 1QP, UK.
SO ONCOGENE, (1999 Dec 23) 18 (56) 8024-32.
Journal code: 8711562. ISSN: 0950-9232.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AJ249344; GENBANK-AJ249345
EM 200002
ED Entered STN: 20000218
Last Updated on STN: 20020420
Entered Medline: 20000204
AB The **serine threonine** kinase protein kinase B regulates cellular activities as diverse as glycogen metabolism and apoptosis. Full activation of protein kinase B requires 3-phosphoinositides and dual phosphorylation on **threonine**-308 and **serine**-473. CaM-K kinase and 3-phosphoinositide dependent-kinase-1 phosphorylate **threonine**-308. **Integrin-linked kinase** reportedly phophorylates **serine**-473. Consistent with this, in a model COS cell system we show that expression of wild-type **integrin-linked kinase** promotes the wortmannin sensitive phosphorylation of **serine**-473 of protein kinase B and its downstream substrates, and inhibits C2-ceramide induced apoptosis. In contrast, **integrin-linked kinase** mutated in a lysine residue critical for function in protein kinases is inactive in these experiments, and furthermore, acts dominantly to block **serine**-473 phosphorylation induced by ErbB4. However, alignment of analogous sequences from different species demonstrates that **integrin-linked kinase** is not a typical protein kinase and identifies a conserved **serine** residue which potentially regulates kinase activity in a phosphorylation dependent manner. Mutation of this **serine** to aspartate or glutamate, but not alanine, in combination with the inactivating lysine mutation restores **integrin-linked kinase** dependent phosphorylation of **serine**-473 of protein kinase B. These data strongly suggest that **integrin-linked kinase** does not possess **serine**-473 kinase activity but functions as an adaptor to recruit a **serine**-473 kinase or **phosphatase**.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
Amino Acid Sequence
COS Cells
Caenorhabditis elegans
Catalytic Domain
Drosophila melanogaster
Molecular Sequence Data
Phosphatidylinositols: ME, metabolism
Phosphorylation
Phosphoserine: ME, metabolism
*Protein-Serine-Threonine Kinases: CH, chemistry
Protein-Serine-Threonine Kinases: GE, genetics
*Protein-Serine-Threonine Kinases: ME, metabolism
Proto-Oncogene Proteins: CH, chemistry
*Proto-Oncogene Proteins: ME, metabolism
Proto-Oncogene Proteins c-raf: CH, chemistry

Recombinant Proteins: CH, chemistry
Recombinant Proteins: ME, metabolism
Sequence Alignment
Sequence Homology, Amino Acid
Transfection
RN 17885-08-4 (Phosphoserine)
CN 0 (Phosphatidylinositols); 0 (Proto-Oncogene Proteins); 0 (Recombinant Proteins); 0 (proto-oncogene protein akt); EC 2.7.1.- (Protein-Serine-Threonine Kinases); EC 2.7.1.- (integrin-linked kinase); EC 2.7.1.37.- (Proto-Oncogene Proteins c-raf)

=> d his

(FILE 'HOME' ENTERED AT 07:33:53 ON 21 JAN 2003)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 07:34:21 ON 21 JAN 2003
E PHOSPHATASE/CN
L1 1 S E3
L2 11938 S PHOSPHATASE
L3 1 S L1 AND L2
L4 11937 S L2 NOT L3
E ILKAP
L5 5 S E3
L6 1 S 473743-92-9
L7 1 S L5 AND L6
L8 4 S L5 NOT L7

FILE 'HCAPLUS' ENTERED AT 07:35:59 ON 21 JAN 2003
L9 1 S L7

FILE 'REGISTRY' ENTERED AT 07:36:57 ON 21 JAN 2003
L10 1 S 473743-91-8
L11 1 S 367924-80-9

FILE 'HCAPLUS' ENTERED AT 07:37:17 ON 21 JAN 2003
L12 1 S L10
L13 2 S L11
L14 2 S L9,L12,L13
E ILKAP
L15 2 S E3
L16 15 S INTEGRIN(L)LINK?(L)?KINASE?(L)ASSOC?(L)?PHOSPHATASE?
L17 8 S L16 (L) SERIN?(L)THREON?
L18 7 S L16 NOT L17
L19 2 S L14,L15
L20 2 S L19 AND L17
L21 6 S L17 NOT L20
L22 4 S L16 AND ILK
L23 5 S L16 AND INTEGRIN LINK? ?KINASE?
L24 5 S L22,L23
L25 2 S L20 AND L24
L26 5 S ILK? AND L12-L25

FILE 'REGISTRY' ENTERED AT 07:46:43 ON 21 JAN 2003
L27 1 S 173585-04-1

FILE 'HCAPLUS' ENTERED AT 07:46:55 ON 21 JAN 2003
L28 99 S L27
L29 3 S L28 AND L12-L26
L30 5 S L24-L26,L29
SEL DN AN L30 1 3 5
L31 2 S L30 NOT E1-E5

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                E LORENS J/AU
L32          29 S E4-E6
                E XU W/AU
L33         423 S E3-E22
                E XU WEI/AU
L34         465 S E3
                E XU WEIDUAN/AU
L35           6 S E3
                E ATCHISON R/AU
L36          16 S E3,E4,E9-E10
                E BOGENBERGER J/AU
L37          27 S E3-E8
                E RIGEL/PA,CS
L38          91 S E3-E19
L39           1 S L32-L38 AND L9,L12-L26,L28-L31
L40           2 S L31,L39
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 07:50:51 ON 21 JAN 2003
L41           4 S E1-E4

     FILE 'BIOSIS' ENTERED AT 07:51:00 ON 21 JAN 2003
L42           0 S L7 OR L10
L43         125 S L27
                E ILKAP
L44           2 S E3
                E ILK
L45           8 S L17
                SEL DN AN 4
L46           1 S L45 AND E1-E2
L47           2 S L44,L46
L48           6 S ILK?(L)ASSOC?(L)?PHOSPHATASE?
L49           2 S L47 AND L48
L50           4 S L43 AND L48
L51           2 S L49,L47
L52           4 S L50 NOT L51
L53           2 S L51 AND L42-L52
                E LORENS J/AU
L54          34 S E3-E6
                E XU W/AU
L55         406 S E3-E22
                E XU WEI/AU
L56         107 S E3
L57           7 S E34
                E ATCHISON R/AU
L58          28 S E3,E5,E9-E11
                E BOGENBERGER J/AU
L59          35 S E3-E7
L60           0 S L43-L53 AND L54-L59

     FILE 'MEDLINE' ENTERED AT 07:57:37 ON 21 JAN 2003
L61           0 S L7 OR L10
                E ILKAP
L62           1 S E3
L63          98 S INTEGRIN? LINK? ?KINASE?
L64          28 S L63 (L) SERIN?(L)THREON?
L65           6 S L64 (L) ?PHOSPHATASE?
                SEL DN AN 4 5 6
L66           3 S E1-E9 AND L65
L67           3 S L62,L66

     FILE 'WPIX' ENTERED AT 08:00:13 ON 21 JAN 2003
                E ILKAP
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L68           0 S L65

     FILE 'BIOTECHDS' ENTERED AT 08:00:39 ON 21 JAN 2003
               E ILKAP
L69           0 S INTEGRIN?(L)LINK?(L)KINASE?(L)PHOSPHATASE(L)SERIN?(L)THREON?

     FILE 'REGISTRY' ENTERED AT 08:01:47 ON 21 JAN 2003

     FILE 'HCAPLUS' ENTERED AT 08:02:01 ON 21 JAN 2003

     FILE 'BIOSIS' ENTERED AT 08:02:36 ON 21 JAN 2003

     FILE 'MEDLINE' ENTERED AT 08:02:43 ON 21 JAN 2003

     FILE 'WPIX' ENTERED AT 08:02:56 ON 21 JAN 2003

     FILE 'BIOTECHDS' ENTERED AT 08:03:40 ON 21 JAN 2003

     FILE 'WPIX' ENTERED AT 08:03:41 ON 21 JAN 2003
               E US2001-284760/AP,PRN
               E WO2002085289/PN
               E LORENS J/AU
L70            4 S E3
               E ATCHISON R/AU
L71            1 S E4
               E BOGENBERGER J/AU
L72            3 S E4
               E XU W/AU
L73          390 S E3-E6
               E RIGEL/PA
L74           59 S E3-E17
L75            5 S L70-L73 AND L74
L76            8 S L70,L71,L72
L77            0 S L76 AND L73
L78            8 S L76,L75
L79            0 S L78 AND (ILK? OR INTEGRIN?)
L80            0 S L70-L74 AND ILK?
L81            2 S L70-L74 AND INTEGRIN
L82            3 S L70-L74 AND ?PHOSPHATASE?
L83            5 S L81,L82
```